UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,385	07/06/2001	Joyce A. Deleo	DC-0156	4729

26259 7590 06/06/2008

LICATA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER	
JAGOE, DONNA A	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
06/06/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/857,385	**Applicant(s)** DELEO ET AL.	
	Examiner Donna Jagoe	**Art Unit** 1614	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 April 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☒ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
    See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

/D. J./
Examiner, Art Unit 1614

Continuation of 11. does NOT place the application in condition for allowance because: Regarding the 112 1st paragraph rejection of claim 1, the rejection is maintained and hereby repeated. The applicant states that "what is conventional or well known to one or ordinary skill in the art need not be disclosed in detail" according to the MPEP §2163. In response, it is not conventional or well known to one of ordinary skill in the art that an agent such as mehtoterxate, administered intrathecally, would infuse into the spinal cord and not the brain with 100 % assurity. Anatomy and Physiology text, Human Anatomy and Physiology, second edition, pages 404-405, provided by Applicant teach that the circulation of the cerebrospinal fluid through the brain ventricles is designed such that only a very small amount of the CSF from the ventricles circulates into the central canal of the spinal cord. Thus, although small, there is circulation and a dose of methotrexate administered intrathecally would circulate into the brain. Regarding the dosage extrapolation, the examiner stands behind the dosage calculation of a rat as 0.8 mg, not 1.25 mg as applicant suggests. To arrive at the correct dosage, one would multiply the dosage of 1 mg/kg by the weight of the animal (0.8kg) (1mg/kg x 0.8kg/1) to arrive at a dosage of 0.8 mg. Applicant appears to be dividing 0.8 into 1 which is incorrect. Applicant states that it is a general principle of pharmacology that if an effectvie dose is taught to be a dose in mg/kg body weight, then in order to extrapolate the dosing of the rat, the species taught in the specification as filed, to a dose that might be used in humans, the species of Chamberlain et al. reference, the dose extrapolation would be done based on consideration of the difference in body weights, not by ignoring the body weight differences". In response, one cannot make sweeping generalizations of dosage extrapolation of all medicaments. Each medicament has it own dosage considerations, toxicities and methods of calculation. Applicants' reliance on the editorial "Body-Surface Area as a bisis for dosing of anticancer agents Science, myth or habit" to allegedly provide evidence that methotrexate is not dosed in this manner is not persuasive. The reference does not have any reference or information drawn to methotrexate contained therein, and therefore is not persuasive. Applicant asserts that the Examiners assessment of the prior art is incorrect with regard to dosing of methotrexate. In response,Jones et al. teach that Methotrexate is a toxic medication, but if it is dosed correctly and monitored appropriately, its toxic effects can be minimized. These effects are categorized as minor or major. Major toxic effects of methotrexate may be life threatening (page 2). Methotrexate should never be given in daily doses. More frequent administration than weekly increases the risk of toxicity. Most patients show a therapeutic response with weekly doses of oral or injection therapy between 7.5 mg and 15.0 mg, although some patients may need 20 or even 30 mg, the maximum recommended dose (pages 5-6). Note that methotrexate is not administered on a mg/kg basis because of the risk of death. It is dosed in mg/m2 or in an empiric dose depending on the malady being treated. In the instant case, if the animal being treated was a human, the dose of 1mg/kg for an 80 kg human (80 mg) would be toxic unless leucovorin rescue was performed. (see official office action mailed 1/29/08. Thus Applicants' arguments drawn to dosing of methotrexate by one of skill in the art are not persuasive.